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Arthur D. Dawson
(Print Name)

Arthur D. Dawson
(Signature)

Date: December 12, 2001

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Thierry Godel, et al.

Serial No.: 09/922,066

Filed: August 03, 2001

Group No.: 1614

COPY OF PAPERS ORIGINALLY FILED

For: **SUBSTITUTED 4-PHENYL-PYRIDINE COMPOUNDS WITH ACTIVITY AS ANTAGONISTS OF NEUROKININ 1 RECEPTORS**

TRANSMITTAL OF CERTIFIED COPY

December 12, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	00117003.4	August 08, 2000

Respectfully submitted,

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Enclosures
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Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

00117003.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

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THE HAGUE, 15/06/01
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Blatt 2 d r Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 00117003.4
Demande n°:

Anmeldetag:
Date of filing: 08/08/00
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Anmelder:
Applicant(s):
Demandeur(s):
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4070 Basel
SWITZERLAND

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
4-Phenyl-pyridine derivatives

In Anspruch genommene Prioriät(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
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Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR
Etats contractants désignés lors du depôt:

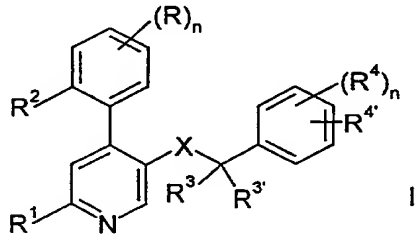
Bemerkungen:
Remarks:
Remarques:

F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 20706

4-Phenyl-pyridine derivatives

The present invention relates to compounds of the general formula

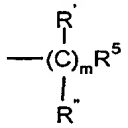


I

wherein

R is hydrogen or halogen;

R^1 is $-(C\equiv C)_mR^{1'}$ or $-(CR'=CR'')_mR^{1'}$
wherein $R^{1'}$ is
a) halogen,
b) cyano, or the following groups:

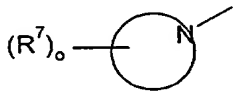


c) ,
d) $-C(O)NR'R''$,
e) $-C(O)O(CH_2)_mR^5$,
f) $-C(O)R^5$,
g) $-N(OH)-(CH_2)_mR^5$,
h) $-NR'C(O)-(CH_2)_mR^5$,
i) $-N[C(O)-R']_2$,
j) $-OR^6$,
k) $-SR^6$, $-S(O)R^6$, or $-S(O)_2R^6$,

l) aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R", nitro, $-(CH_2)_nOR'$, -C(O)NR'R", -C(O)OR' or –C(O)R',

m) is a five or six membered heteroaryl group, containing one to four heteroatoms, selected from N, O or S and may be optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R", nitro, $-(CH_2)_nOR'$, -C(O)OR', -C(O)NR'R" or –C(O)R',

n) is a five or six membered saturated cyclic tertiary amine of the group



which may contain one additional heteroatom, selected from N, O or S,

R'/R" are independently from each other hydrogen, lower alkyl, cycloalkyl or aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'"R"", nitro, $-(CH_2)_nOR'''$, -C(O)NR'"R"", -C(O)OR'" or –C(O)R'",

R'"/R"" are independently from each other hydrogen, lower alkyl, cycloalkyl or aryl,

R^5 is hydrogen, cyano, hydroxy, halogen, trifluoromethyl, -C(O)OR' or aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R", nitro, $-(CH_2)_nOR'$, -C(O)NR'R", -C(O)OR' or –C(O)R', or is a five or six membered heteroaryl group, containing one to four heteroatoms, selected fron N, O or S and may be optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R", nitro, $-(CH_2)_nOR'$, -C(O)NR'R", -C(O)OR' or –C(O)R',

R^6 is hydrogen, lower alkyl, trifluoromethyl, or aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R", nitro, -C(O)NR'R", $-(CH_2)_nOR'$, -C(O)OR' or –C(O)R', or is a five or six membered heteroaryl group, containing one to four heteroatoms, selected fron N, O or S and may be optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R", nitro, $-(CH_2)_nOR'$, -C(O)NR'R", -C(O)OR' or –C(O)R',

R^7 is $-C(O)-(CH_2)_mOH$ or an oxo group;

R^2 hydrogen, lower alkyl, lower alkoxy, halogen or CF_3;

$R^3/R^{3'}$ are independently from each other hydrogen, lower alkyl or form together with the carbon atom to which they are attached a cycloalkyl group;

$R^4/R^{4'}$ are independently from each other hydrogen, halogen, CF_3, lower alkyl or lower alkoxy;

R and R^2 or R^4 and $R^{4'}$ may be together –CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl, halogen or lower alkoxy;

X is $-C(O)N(R^8)-$, $(CH_2)_pO-$, $-(CH_2)_pN(R^8)-$, $-N(R^8)C(O)-$ or $-N(R^8)-(CH_2)_p-$; wherein R^8 is hydrogen or lower alkyl;

n is 1 or 2;
m is 0 to 4;
o is 1 or 2; and
p is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I and their salts are characterized by valuable therapeutic properties. It has been surprisingly found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The receptor for substance P is a member of the superfamily of G protein-coupled receptors.

The neuropeptide receptor for substance P (NK-1) is widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes.
The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine

withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993.

Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting.

In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.

The usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is further described in "Neuropeptides, 32(1), 1-49, (1998)" and "Eur. J. Pharmacol., 383(3), 297-303, (1999)".

The compounds of formula I can also be used in form of their prodrugs. Examples are esters, N-oxides, phosphate esters, glycoamide esters, glyceride conjugates and the like. The prodrugs may add to the value of the present compounds advantages in adsorption, pharmacokinetics in distribution and transport to the brain.

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1 - 4 carbon atoms.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3 – 6 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above, and which is attached via an oxygen atom.

The term "five or six membered heteroaryl group, containing one to four heteroatoms, selected from N, O or S" denotes, for example, the following groups: pyrrol-1-yl, imidazol-1 or 2-yl, pyrazol-1-yl, pyridin-2, 3 or 4–yl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, thienyl or furyl.

The term "five or six membered saturated cyclic tertiary amine" denotes, for example, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiomorpholin-1,1-dioxo or thiomorpholin-1-oxo.

The term "aryl" denotes a monocyclic aromatic hydrocarbon radical or a bicyclic or tricyclic ring system in which at least one ring is aromatic, preferred are phenyl or naphthyl rings.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders or emesis by the administration of NK-1 receptor antagonists. A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities.

Preferred are compounds of formula I, in which X is $-C(O)N(CH_3)-$ and $-(R^4)_n$ is 3,5-di-CF_3. Exemplary preferred compounds of this group are those, wherein $R^3/R^{3'}$ are both hydrogen and R^2 is methyl, for example the following compounds:

N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-hydroxyacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-cyanomethyl-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-iodo-N-methyl-4-o-tolyl-nicotinamide,
4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridine-2-carboxylic acid methyl ester or
N-(3,5-bis-trifluoromethyl-benzyl)-6-hydroxymethyl-N-methyl-4-o-tolyl-nicotinamide.

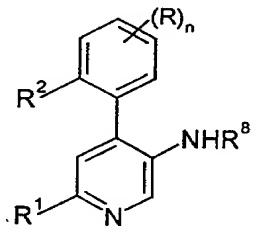
Further preferred are compounds of formula I, in which X is $-N(CH_3)C(O)-$ and $-(R^4)_n$ is 3,5-di-CF_3. Exemparly preferred compounds of this group are those, wherein $R^3/R^{3'}$ are both methyl and R^2 is methyl, for example the following compounds:

2-(3,5-bis-trifluoromethyl-phenyl)-N-{6-[hydroxy-(2-hydroxy-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
acetic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-acetylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(hydroxyacetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2,5-dioxo-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide or
cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-cyclopropanecarbonyl-amide.

Preferred compounds of this group are further those, wherein $R^3/R^{3'}$ are both hydrogen and R^2 is chloro, for example the following compounds:
2-(3,5-bis-trifluoromethyl-phenyl)-N-{4-(2-chloro-phenyl)-6-[hydroxy-(2-hydroxy-ethyl)-amino]-pyridin-3-yl}-N-methyl-isobutyramide or
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(3-oxo-morpholin-4-yl)-pyridin-3-yl]-N-methyl-isobutyramide.

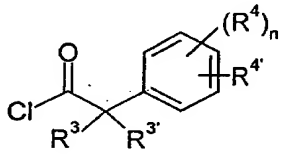
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



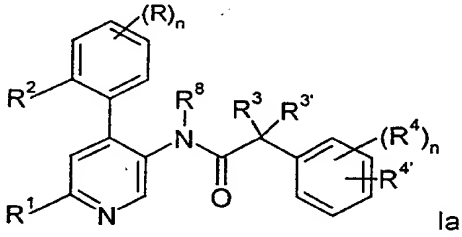
II

with a compound of formula



III

to a compound of formula

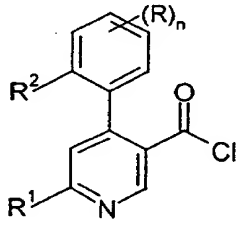


Ia

wherein R^1- R^4, R and n have the significances given above,

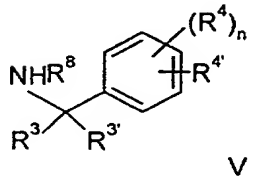
or

b) reacting a compound of formula



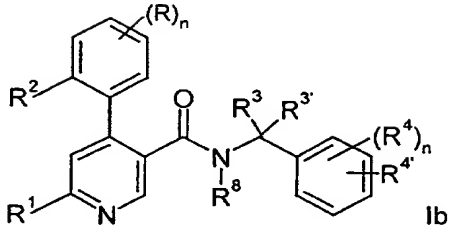
IV

with a compound of formula



V

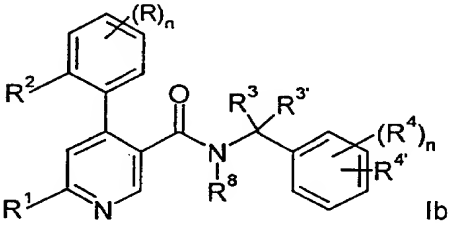
to give a compound of formula



Ib

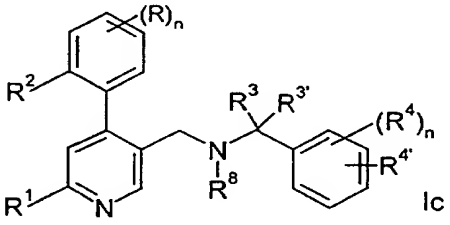
wherein R^1-R^4, R and n have the significances given above, or

c) reducing a compound of formula



Ib

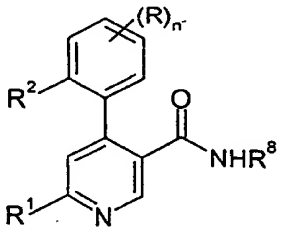
to a compound of formula



Ic

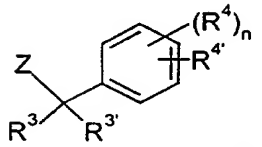
wherein the definition of substituents is given above, or

d) reacting a compound of formula



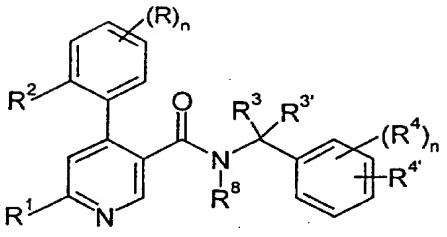
VI

with a compound of formula



VII

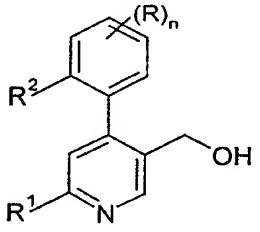
to a compound of formula



Ib

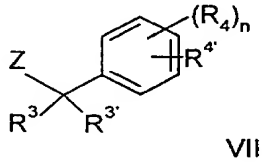
wherein Z is Cl, Br, I, $-OS(O)_2CH_3$ or $-OS(O)_2C_6H_4CH_3$ and the other definitions of substituents are given above, or

e) reacting a compound of formula



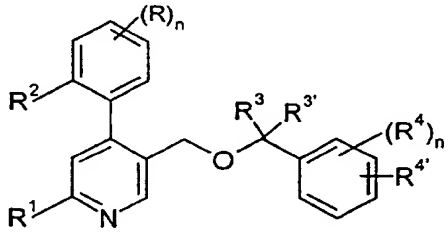
VIII

with a compound of formula



VII

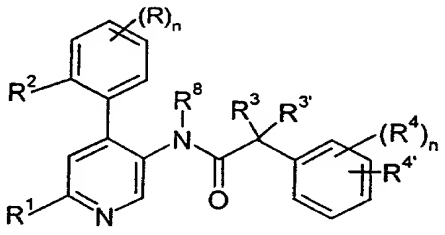
to a compound of formula



Id

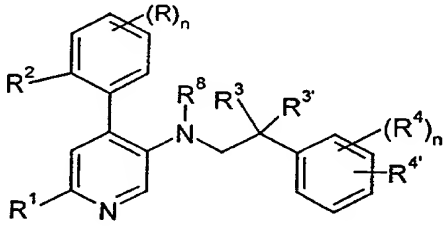
wherein Z is Cl, Br, I,- $OS(O)_2CH_3$ or $-OS(O)_2C_6H_4CH_3$ and the definition of the other substituents is given above, or

f) reducing a compound of formula



Ia

to a compound of formula



Ie

wherein the definition of substituents is given above,

or

h) modifying one or more substituents R^1-R^4, R^8 or R within the definitions given above, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

In accordance with process variant a) DIPEA (N-ethyldiisopropyl-amine) is added to a mixture of a compound of formula II and of a compound of formula III in dichloromethane and the mixture is stirred at temperatures between 25-40°C. The desired compound of formula Ia is isolated after purification in good yields.

Process variant b) describes the reaction of a compound of formula IV with a compound of formula V to a compound of formula Ib. The reaction is carried out in conventional manner, for example in a solvent, such as a mixture of toluene and triethyl-amine. The mixture is refluxed for about 1 hour.

In accordance with process variant c) a compound of formula Ib is reduced to a compound of formula Ic. This reaction is carried out with a reducing agent, such as $LiAlH_4$ or BH_3•THF, in conventional manner.

Process variant d) describes the reaction of a compound of formula VI with a compound of formula VII to a compound of formula Ib. This reaction is carried out by deprotonation of a compound of formula VI with KHMDS (potassium hexamethyldisilazide) and subsequent addition of a compound of formula VII. A suitable solvent is tetrahydrofuran. The reaction is carried out at room temperature.

In accordance with process variant e) a compound of formula Id is prepared. This reaction is carried out by deprotonation of a compound of formula VIII with NaH and susequent addition of a compound of formula VII. This reaction is carried out in conventional manner.

A further method for the preparation of a compound of formula I is described in process variant f). A compound of formula Ia is reduced to a compound of formula Ie in conventional manner, for example with $LiAlH_4$ or BH_3•THF.

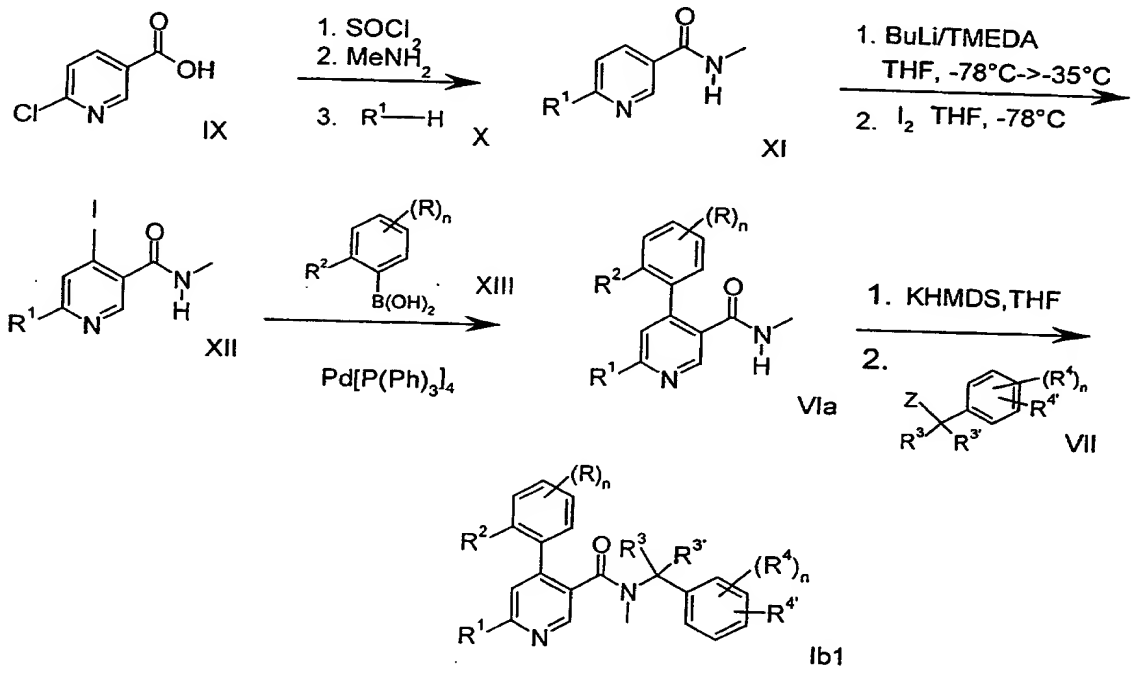
The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

The following schemes 1-8 describe the processes for preparation of compounds of formula I in more detail. The starting materials are known compounds or may be prepared according to methods known in the art.

In the schemes the following abbreviations have been used:

PivCl	pivaloyl chloride
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylene diamine
DIPEA	N-ethyldiisopropyl-amine
KHMDS	potassium hexamethyldisilazide

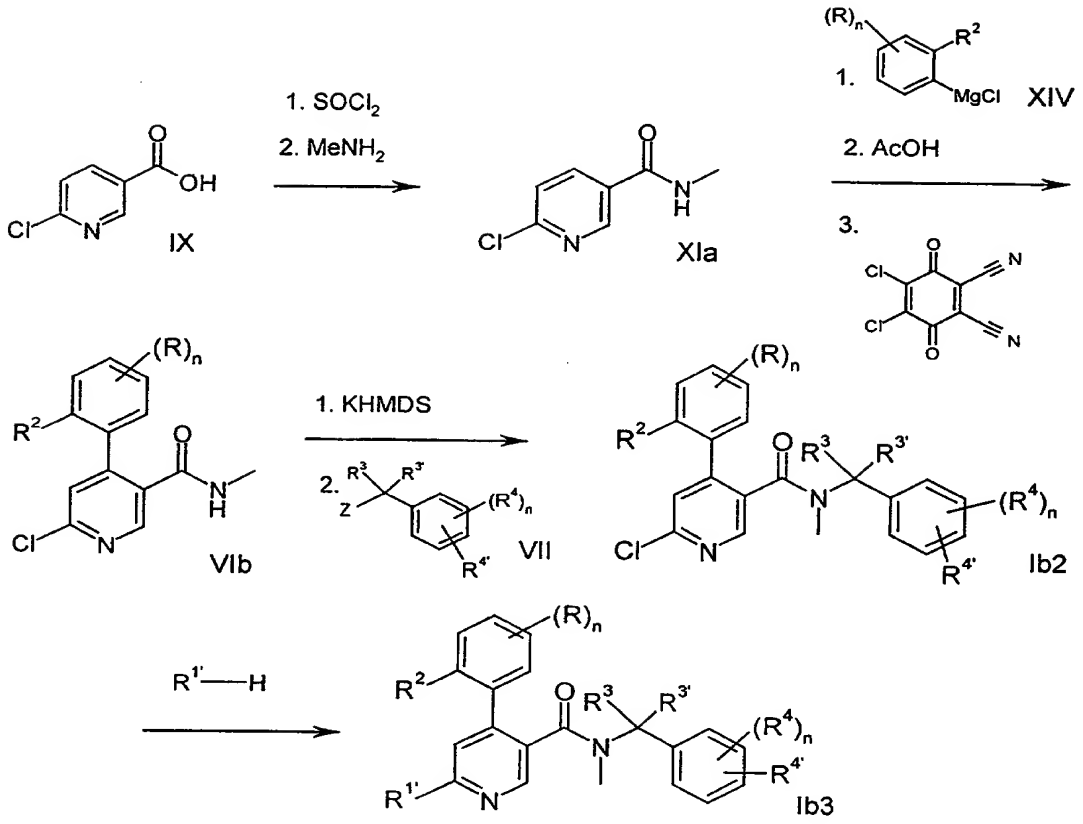
Scheme 1



Z = Cl, Br, I or $OS(O)_2C_6H_4CH_3$ or $OS(O)_2CH_3$

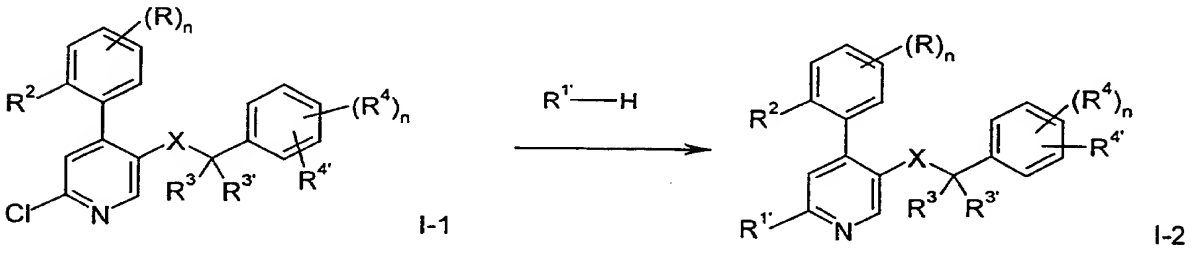
The substituents are described above.

Scheme 2



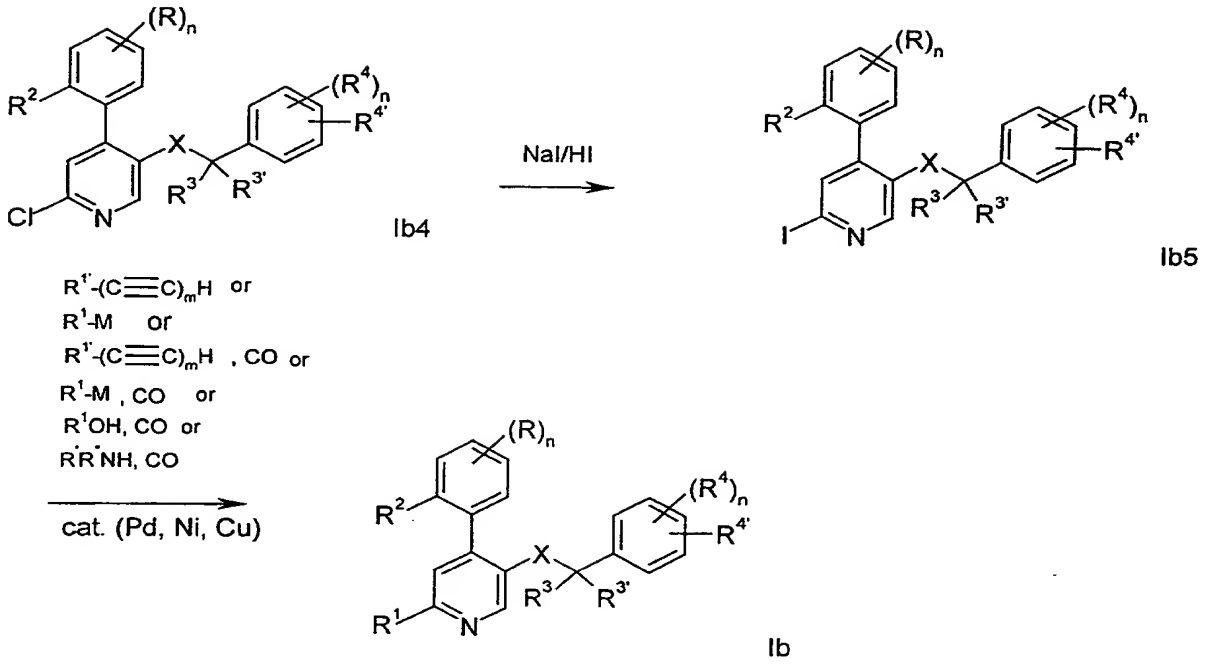
The substituents have the significances given above. $R^{1'}$ may be the same as for R^1, with the exception of chloro.

Scheme 3



The substituents have the significances given above. $R^{1'}$ may be the same as for R^1, with the exception of chloro.

Scheme 4

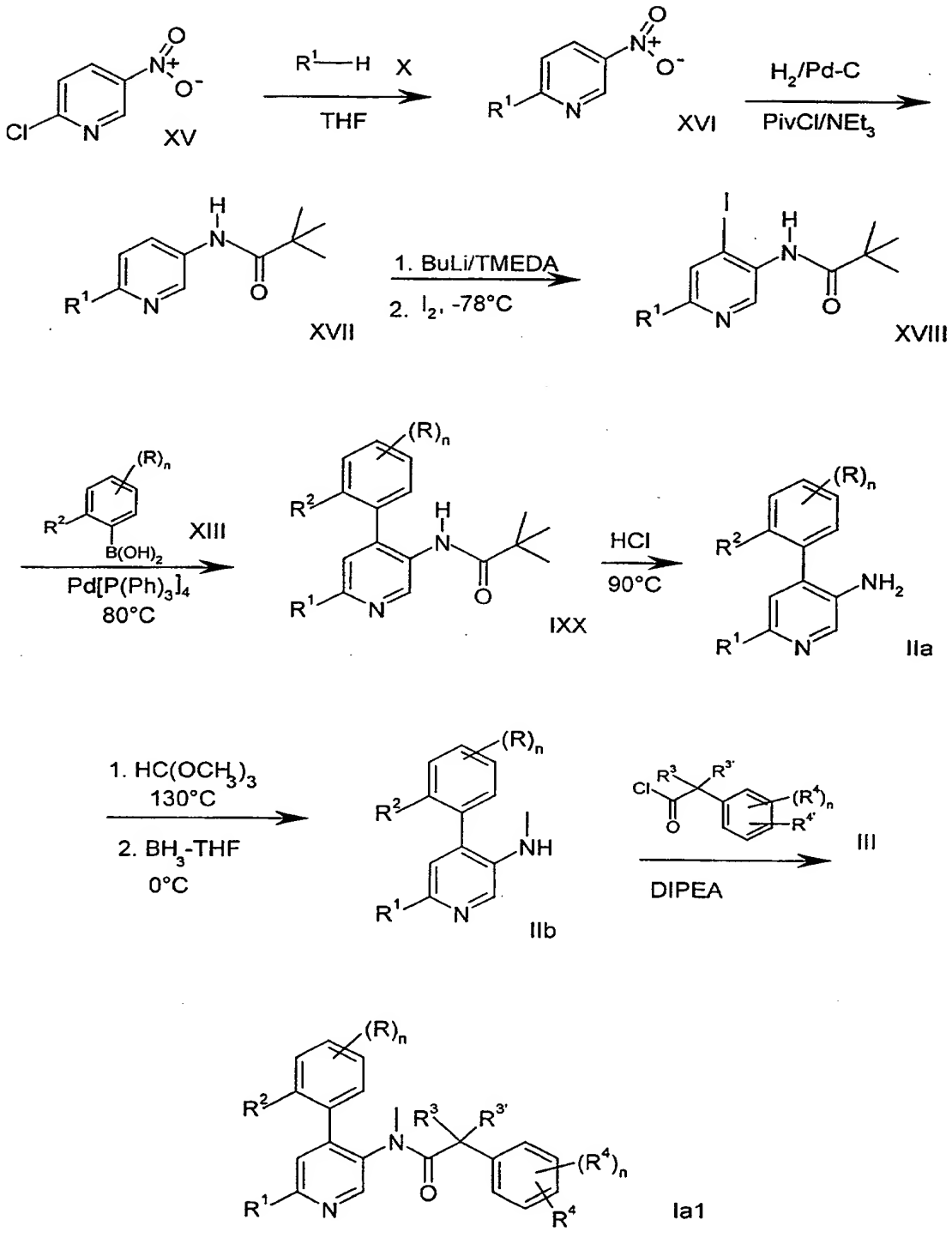


M=9-BBN, $B(OR')_2$, SnR'_3, MgZ, ZnZ

Z=Cl, Br or Iod

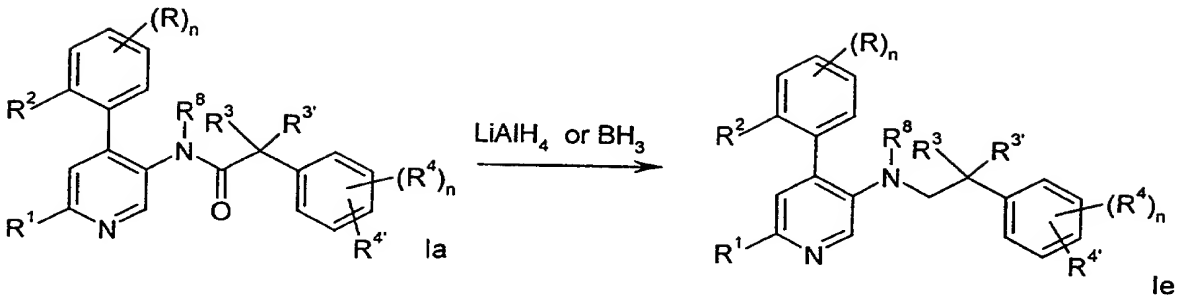
9-BBN is 9-borabicyclo[3.3.1]nonyl and the other substituents have the significances given above.

Scheme 5



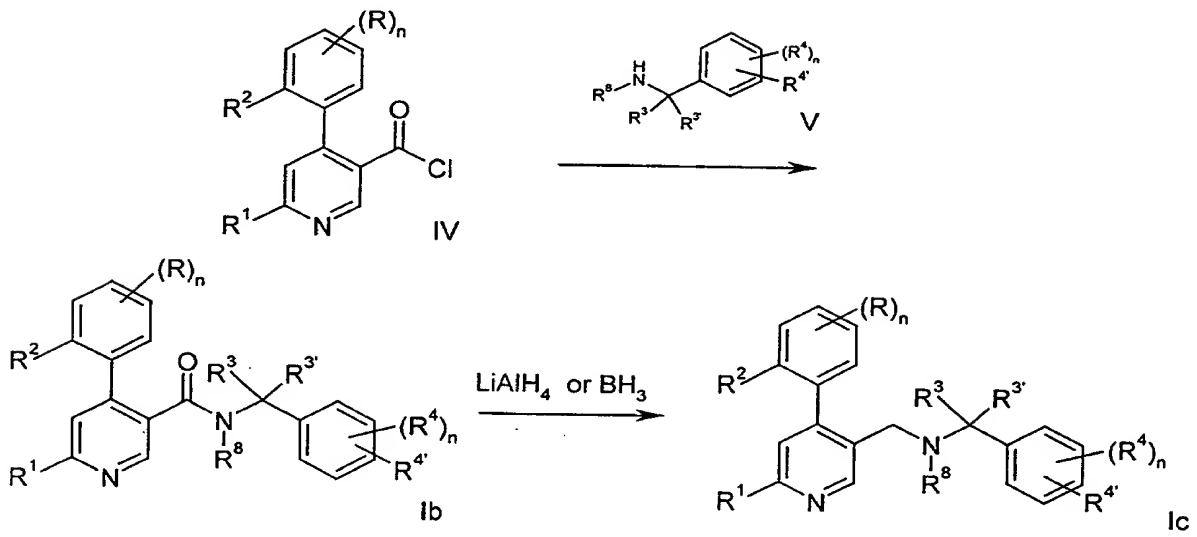
The substituents have the significances given above.

Scheme 6



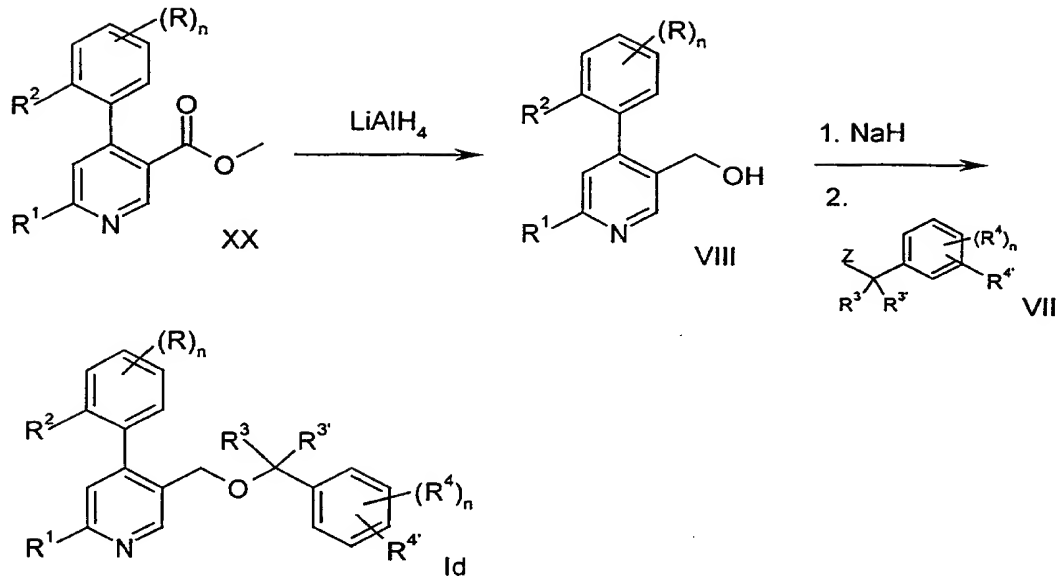
The substituents have the significances given above.

Scheme 7



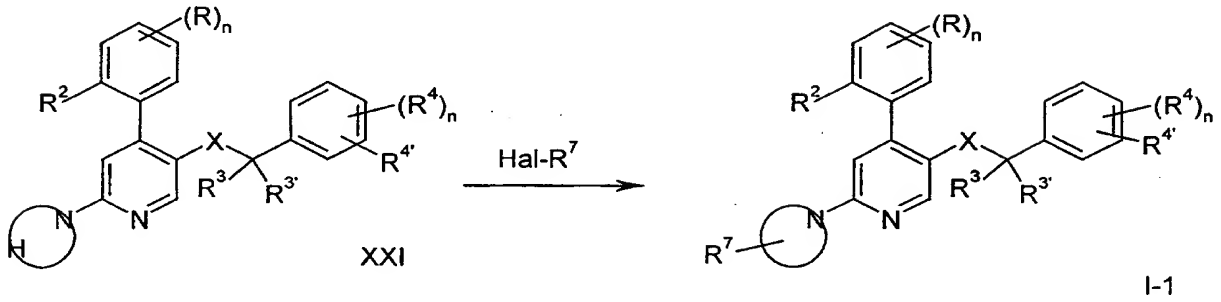
The substituents have the significances given above.

Scheme 8



The substituents have the significances given above.

Scheme 9



The substituents have the significances given above.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor.

The compounds were investigated in accordance with the tests given hereinafter.

The affinity of test compounds for the NK_1 receptor was evaluated at human NK_1 receptors in CHO cells infected with the human NK_1 receptor (using the Semliki virus expression system) and radiolabelled with [^{3}H]substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04

%) leupeptin (8 µg / ml), $MnCl_2$ (3mM) and phosphoramidon (2 µM). Binding assays consisted of 250 µl of membrane suspension ($1.25x10^5$ cells / assay tube), 0.125 µl of buffer of displacing agent and 125 µl of [^{3}H]substance P. Displacement curves were determined with at least seven concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under vacuum through GF/C filters presoaked for 60 min with PEI (0.3%) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in triplicate in at least 2 separate experiments.

The affinity to the NK-1 receptor, given as pKi, is in the scope of 7.90 - 9.50 for the described compounds.

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying

the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

Example 1

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-hydroxyacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide

a) 6-Chloro-N-methyl-nicotinamide

To 50 g (317 mmol) of 2-chloronicotinic acid was added 230 ml (3.16 mol) thionyl chloride at 0°C. After heating the mixture at reflux for 2h excess thionyl chloride was removed by distillation. The oily brown residue was dissolved in 250 ml dichloromethane. The solution was treated with methylamine gas at 0°C until no exothermic reaction was observed any longer. The resulting suspension was diluted with 1000 ml dichloromethane/water. The layers were separated and the aqueous layer extracted with three 300 ml portions of dichloromethane. Drying of the organic layer with sodium sulfate and concentration gave 53.2 g (98%) of the title compound as a light yellow solid.

MS m/e (%): 171 ($M+H^+$, 15).

b) 6-Chloro-N-methyl-4-o-tolyl-nicotinamide

To a solution of 3.41 g (20.0 mmol) 6-chloro-N-methyl-nicotinamide in 80 ml tetrahydrofuran 50 ml (50 mmol) of a 1 M solution of o-tolyl magnesium chloride in tetrahydrofuran was added dropwise at 0°C. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 1.5h. The mixture was again cooled to 0°C, followed by the dropwise addition of 5.7 ml (100 mmol) acetic acid and a solution of 5.1 g (22 mmol) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 18 ml tetrahydrofuran. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 15 min. Addition of 30 ml 2 N aqueous sodium hydroxide solution was followed by dilution with 1 l ethyl acetate and 200 ml water. The layers were separated and the organic washed with 4 250-ml portions of 2 N aqueous

sodium hydroxide solution. The combined aqueous layers were extracted with 3 500-ml portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium chloride solution and dried with sodium sulfate. Concentration gave 5.44 g of a brown-red oil. Flash column chromatography afforded 2.15 g (41.3%) of the title compound as a light yellow solid.

MS m/e (%): 260 ($M^{\cdot+}$, 11). M.p. 91 – 93°C.

c) 4-(5-Methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 8.31 g (31.9 mmol) 6-chloro-N-methyl-4-o-tolyl-nicotinamide, 6.53 g (35.0 mmol) 1-tert-butoxycarbonyl piperazine, 16.7 ml (95.6 mmol) N-ethyldiisopropylamine and a catalytic amount of 4-(N,N-dimethylamino)-pyridine was heated at reflux over night. After cooling to room temperature the mixture was dissolved in dichloromethane and washed with two portions of 0.1 M aqueous hydrochloric acid solution. Drying with sodium sulfate and concentration gave 10.7 g of the crude product. Flash column chromatography afforded 6.28 g (48.0%) of the title compound as an off-white solid.

MS m/e (%): 411 ($M+H^+$, 100).

d) 4-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 6.28 g (15.3 mmol) 4-(5-methylcarbamoyl-4-o-tolyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 250 ml tetrahydrofuran 20 ml of a 1 M solution (20 mmol) of potassium hexamethyldisilazide in tetrahydrofuran were added at 0°C. After 30 min, 2.81 ml (15.3 mmol) 3,5-bis(trifluoromethyl)benzyl bromide were added dropwise. The reaction mixture was allowed to warm to room temperature over night. Addition of water and 1 M aqueous sodium hydroxide solution was followed by extraction with three portions of ethyl acetate. The combined organic extracts were dried with sodium sulfate and concentrated. Flash column chromatography gave 6.89 g (70.8%) of the title compound as a white solid.

MS m/e (%): 637 ($M+H^+$, 100).

e) N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide

To a solution of 6.60 g (104 mmol) 4-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-piperazine-1-carboxylic acid tert-butyl ester and 8.40 ml (207 mmol) methanol in 50 ml ethyl acetate 14.7 ml (207 mmol) acetyl chloride were

added dropwise at 0°C. After 4h the reaction mixture was diluted with ethyl acetate and treated with 1 M sodium hydroxide solution. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried with sodium sulfate and concentrated to give 5.36 g of crude product. Flash column chromatography afforded 4.86 g (87.4%) of the title compound as a light brown solid.

MS m/e (%): 537 ($M+H^+$, 100).

f) N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-bromoacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide

To a solution of 0.30 g (0.56 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-piperazin-1-yl-4-o-tolyl-nicotinamide in 4 ml dichloromethane 0.055 ml (0.62 mmol) bromoacetyl bromide and 4 ml of a 2M aqueous sodium carbonate solution were consecutively added dropwise at 10°C. After 2h the reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was dried with sodium sulfate and concentrated to give 0.36 g of crude product. Flash column chromatography afforded 0.26 g (69%) of the title compound as a white solid.

MS m/e (%): 657 ($M+H^+$, 100, 1 Br).

g) N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-hydroxyacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide

A mixture of 0.12 g (0.18 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-bromoacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide, 1.2 ml 1-methyl-2-pyrrolidone and 0.2 ml half-saturated aqueous sodium bicarbonate solution was stirred at 100°C over night. After cooling to room temperature and dilution with water the mixture was extracted with five portions of tert-butyl methyl ether. The combined organic extracts were dried with sodium sulfate, concentrated and dried in vacuo (0.5 mbar) at 70 °. Flash column chromatography afforded 71 mg (64%) of the title compound as a white solid.

MS m/e (%): 595 ($M+H^+$, 100).

Example 2

N-(3,5-Bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide

To a solution of 10.0 g (38.4 mmol) 6-chloro-N-methyl-4-o-tolyl-nicotinamide in 190 ml tetrahydrofuran 46 ml of a 1 M solution (46 mmol) of potassium hexamethyldisilazide in tetrahydrofuran were added at 0°C. After 30 min, 8.5 ml (46 mmol) 3,5-bis(trifluoromethyl)benzyl bromide were added dropwise to the resulting suspension.

After completed addition the ice-water cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 2h the reaction was quenched with water. The mixture was adjusted to pH 3 with 1 M aqueous hydrochloric acid solution and stirred for 10 min. Basification with 1 M aqueous sodium hydroxide solution to pH 8 was followed by concentration to remove tetrahydrofuran. The aqueous residue was extracted with four portions of dichloromethane. The combined organic extracts were dried with sodium sulfate and concentrated to give 21.4 g of crude product. Column chromatography afforded 18.4 g (98.5%) of the title compound as a white solid.

MS m/e (%): 485 ($[M-H]^+$, 2).

Example 3

N-(3,5-Bis-trifluoromethyl-benzyl)-6-cyanomethyl-N-methyl-4-o-tolyl-nicotinamide

a) (RS)-{5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-cyano-acetic acid ethyl ester

A mixture of 1.00 g (2.05 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide, 0.44 ml (4.1 mmol) ethyl cyanoacetate and 0.46 g (4.1 mmol) potassium tert-butoxide in 2 ml dimethyl sulfoxide was stirred at 100°C over night. After cooling to room temperature 10 ml of a half-concentrated aqueous solution of ammonium chloride was added. The mixture was extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with two portions of water, dried with sodium sulfate and concentrated to give 1.2 g of crude product. Flash chromatography afforded 0.681 g (58.8%) of the title compound as a yellow foam.

MS m/e (%): 563 ($M^{\cdot+}$, 80).

b) N-(3,5-Bis-trifluoromethyl-benzyl)-6-cyanomethyl-N-methyl-4-o-tolyl-nicotinamide

A mixture of 650 mg (1.15 mmol) (RS)-{5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridin-2-yl}-cyano-acetic acid ethyl ester and 0.20 g (4.6 mmol) lithium chloride in wet dimethyl sulfoxide was stirred at 120°C over night. After cooling the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The layers were separated and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic extracts were washed with two portions of water, dried with magnesium sulfate and concentrated to give 595 mg of crude product. Flash chromatography afforded 396 mg (69.9%) of the title compound as a white solid.

MS m/e (%): 492 ($M+H^+$, 100).

Example 4

N-(3,5-Bis-trifluoromethyl-benzyl)-6-iodo-N-methyl-4-o-tolyl-nicotinamide

To a solution of 1.00 g (2.05 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide in 10 ml 2-butanone 1.1 g (7.2 mmol) sodium iodide and 0.28 ml (2.1 mmol) hydroiodic acid (57% in water) were added at room temperature. The mixture was heated at 80°C for 2h. After cooling to room temperature the mixture was diluted with ethyl acetate and treated with saturated aqueous sodium bicarbonate solution. The layers were separated, the organic layer washed with water, dried with magnesium sulfate and concentrated to give 1.5 g of crude product. Flash column chromatography gave 1.11 g (93.6%) of the title compound as a yellow oil.

MS m/e (%): 579 ($M+H^+$, 100).

Example 5

4-o-Tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

A mixture of 100 mg (0.173 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-iodo-N-methyl-4-o-tolyl-nicotinamide, 21 mg (0.17 mmol) 4-pyridylboronic acid, 5 ml dimethoxyethane and 5 ml of a 2 M aqueous solution of sodium carbonate was deoxygenated by three freeze-thaw cycles. After addition of 20 mg (0.017 mmol) tetrakis(triphenylphosphine)palladium(0) the reaction mixture was stirred at 90°C for 60h. Cooling to room temperature was followed by dilution with water and extraction with 3 portions of ethyl acetate. The organic extract was washed with water, dried with magnesium sulfate and concentrated. Column chromatography afforded 59 mg (64%) of the title compound as a yellow solid.

MS m/e (%):530 ($M+H^+$, 100).

Example 6

5-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridine-2-carboxylic acid methyl ester

A solution of 690 mg (1.19 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-iodo-N-methyl-4-o-tolyl-nicotinamide, 0.33 ml (2.4 mmol) triethylamine and 1.9 ml (48 mmol) methanol in 10 ml N,N-dimethylformamide was deoxygenated by three freeze-thaw cycles. Filling

the flask with carbon monoxide gas from a balloon was followed by addition of 31 mg (0.12 mmol) triphenylphosphine and 23 mg (0.012 mmol) palladium(II) acetate. The reaction mixture was stirred for 60h under an atmosphere of carbon monoxide gas at room temperature. The mixture was diluted with water and extracted with 3 portions of tert-butyl methyl ether. The combined organic extracts were washed with water, dried with sodium sulfate and concentrated. Flash chromatography afforded 407 mg (66.8%) of the title compound as a light-yellow solid.

MS m/e (%): 511 ($M+H^+$, 100).

Example 7

N-(3,5-Bis-trifluoromethyl-benzyl)-6-hydroxymethyl-N-methyl-4-o-tolyl-nicotinamide

To a solution of 9 mg (4 mmol) lithium borohydride in 0.5 ml diethyl ether was added a solution of 346 mg (0.678 mmol) 5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridine-2-carboxylic acid methyl ester in 0.6 ml toluene. The mixture was gradually heated to 100°C, whereby diethyl ether was distilled off. After heating for 2h at 100°C the resulting suspension was concentrated. The residue was treated with 5 ml of a 1 M aqueous solution of hydrochloric acid for 5 min. Basification with potassium carbonate was followed by extraction with tert-butyl methyl ether. The combined organic extracts were dried with sodium sulfate and concentrated. Flash chromatography afforded 240 mg (73.4%) of the title compound as a light brown oil.

MS m/e (%): 481 ($M-H^-$, 6).

Example 8

2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[hydroxy-(2-hydroxy-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide

a) 4-(5-Nitro-2-pyridyl)-morpholine

To a solution of 20 g (126 mmol) of 2-chloro-5-nitropyridine in 150 ml tetrahydrofuran were added dropwise 27 ml (315 mmol) morpholine within 10 min. The reaction mixture was refluxed for additional 2 h. After cooling to room temperature, the solvent was removed in vacuo and the residue was re-dissolved in 200 ml ethyl acetate. The organic phase was washed with 200 ml 1 N sodium bicarbonate solution, dried (magnesium sulfate) and evaporated to give 27.3 g (quantitative) of the title compound as a yellow solid. M.p. 142-143°C.

b) 2,2-Dimethyl-N-(6-morpholin-4-yl-pyridin-3-yl)-propionamide

To a solution of 27.3 g (126 mmol) of 4-(5-nitro-2-pyridyl)-morpholine in 600 ml methanol were added 2.5 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature to ca. 45°C, 1 bar) until the theoretical amount of hydrogen was taken up (about 3 h). The catalyst was filtered off and was washed twice with 100 ml portions of methanol. The filtrate was evaporated in vacuo to give 22.6 g of a purple oil which consisted to ca. 95 % of the desired aniline derivative according to analysis by thin layer chromatography.

This crude product was dissolved in a mixture of 240 ml tetrahydrofuran and 60 ml diethyl ether. After cooling to 0°C, 26 ml (189 mmol) of triethylamine were added in one portion. Stirring was continued while 23 g (189 mmol) of pivaloyl chloride were added dropwise within a period of 10 min. The ice bath was removed and the reaction mixture was stirred for 1 h at room temperature. Then, the solvent was removed in vacuo and the residue was suspended in 200 ml 1 N sodium bicarbonate solution. The product was extracted three times with 200 ml portions of dichloromethane, dried (sodium sulfate) and evaporated. Recrystallization of the solid residue from ethyl acetate/hexane 1:8 gave 28.6 g (86%) of the title compound as white crystals.

MS m/e (%): 264 ($M+H^+$, 100).

c) N-(4-Iodo-6-morpholin-4-yl-pyridin-3-yl)-2,2-dimethyl-propionamide

A solution of 28.4 g (108 mmol) 2,2-dimethyl-N-(6-morpholin-4-yl-pyridin-3-yl)-propionamide and 49 ml (324 mmol) N,N,N',N'-tetramethylethylenediamine under argon in 600 ml tetrahydrofuran was cooled in a dry ice bath to -78°C. Within 1 h, 202 ml (324 mmol) of a 1.6 N n-butyllithium solution in hexane were added dropwise. The reaction mixture was allowed to warm up to -35°C overnight. After cooling again to -78°C, 37 g (146 mmol) iodine dissolved in 60 ml tetrahydrofuran were added dropwise during 15 min. The dry ice bath was replaced by an ice bath and a solution of 90 g (363 mmol) sodium thiosulfate pentahydrate in 250 ml water were added within 10 min when the temperature of the reaction mixture had reached 0°C. Then, 1000 ml diethyl ether were added and the organic layer was separated. The aqueous layer was extracted twice with 500 ml dichloromethane and the combined organic layers were dried (magnesium sulfate) and evaporated. Flash chromatography gave 15.6 g (37%) of the title compound as a light brown oil which crystallized upon standing at room temperature.

MS m/e (%): 389 (M^+, 71), 358 (25), 304 (43), 57 (100).

d) 2,2-Dimethyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-propionamide

A mixture of 3.50 g (9.0 mmol) N-(4-iodo-6-morpholin-4-yl-pyridin-3-yl)-2,2-dimethyl-propionamide, 35 ml toluene, 18 ml 2 N sodium carbonate solution, 312 mg (0.27 mmol) tetrakis(triphenylphosphine)palladium(0) and 1.34 g (9.9 mmol) o-tolylboronic acid was heated under argon at 80°C for 12 h. After cooling to room temperature, the aqueous phase was separated and washed twice with ethyl acetate. The combined organic layers were washed with 50 ml brine, dried (sodium sulfate) and evaporated. Purification by flash-chromatography gave 3.23 g (quantitative) of the title compound as a white foam.

MS m/e (%): 354 ($M+H^+$, 100).

e) 6-Morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine

A suspension of 2.93 g (8.28 mmol) 2,2-dimethyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-propionamide in 80 ml 3 N hydrochloric acid solution and 5 ml 1-propanol was heated to 90-95°C overnight. The reaction mixture was cooled to room temperature, washed with three 20 ml portions diethyl ether and filtered over celite. The filtrate was diluted with 20 ml water and was adjusted to pH 7-8 by addition of 28 % sodium hydroxide solution under ice cooling. The product was extracted with four 100 ml portions of dichloromethane. The combined organic layers were washed with 50 ml brine, dried (magnesium sulfate) and evaporated to give 2.31 g (quantitative) of the title compound as a white foam.

MS m/e (%): 269 (M^+, 100).

f) Methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine

A solution of 2.24 g (8.3 mmol) 6-morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine in 17 ml trimethyl orthoformate and 3 drops trifluoroacetic acid was heated for 2 h at 130°C. The reaction mixture was evaporated and dried in vacuo for 30 min. The residual oil was dissolved in 5 ml tetrahydrofuran and was added dropwise under ice cooling to 630 mg (16.6 mmol) lithium aluminum hydride in 20 ml tetrahydrofuran. The reaction mixture was stirred for 1 h at room temperature, cooled to 0°C again and acidified (pH 1-2) by addition of 28 % hydrochloric acid solution. After stirring for 5 min, 28 % sodium hydroxide solution was added to reach pH 10. The solution was filtered over celite, evaporated and purified by flash chromatography to give 1.56 g (66%) of the title compound as a white foam.

MS m/e (%): 283 (M^+, 100).

g) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide

A solution of 1.46 g (5.15 mmol) methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine and 1.32 ml (7.73 mmol) N-ethyldiisopropylamine in 15 ml dichloromethane was cooled in an ice bath and 1.8 g (5.67 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride were added dropwise. The reaction mixture was warmed to 35-40°C for 3 h, cooled to room temperature again and was stirred with 25 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 2.9 g (quantitative) of the title compound as white crystals. M.p. 131-132°C.

h) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

A mixture of 1.0 g (1.76 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide, 100 mg (0.48 mmol) ruthenium(III)chloride hydrate, 832 mg (3.87 mmol) sodium periodate, 3.5 ml carbon tetrachloride, 3.5 ml acetonitrile and 5.3 ml water was stirred for 4 days at room temperature. Dichloromethane was added, the organic layer was separated, washed with sodium hydrogensulfite solution and filtered over celite. To the filtrate were added 10 ml 1 N potassium hydroxide solution and 20 ml methanol. After heating the mixture for 1 h at 40°C, the solvents were removed in vacuo and the residue was purified by flash-chromatography to give 352 mg (37%) of the title compound as light brown foam.

MS m/e (%): 540 ($M+H^+$, 100).

i) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-{6-[hydroxy-(2-hydroxy-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide

To a solution of 500 mg (0.93 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide in 5 ml dichloromethane was added under ice cooling a solution of 240 mg (0.97 mmol) of 3-chloroperbenzoic acid (*ca.* 70 %) in 5 ml dichloromethane. After stirring for 2 h at 0°C, the reaction mixture was washed twice with saturated sodium carbonate solution, dried (sodium sulfate) and evaporated. The crude material was suspended in a mixture of dichloromethane and hexane, filtered and dried *in vacuo* to give 345 mg (62%) of the title compound as white crystals.

MS m/e (%): 556 ($M+H^+$, 100).

Example 9

2-(3,5-Bis-trifluoromethyl-phenyl)-N-{4-(2-chloro-phenyl)-6-[hydroxy-(2-hydroxy-ethyl)-amino]-pyridin-3-yl}-N-methyl-isobutyramide

The title compound was obtained as light brown foam in comparable yield according to the procedure described above for the preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-{6-[hydroxy-(2-hydroxy-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide using 2-chlorophenylboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 576 ($M+H^+$, 100).

Example 10

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide

To an ice-cooled suspension of 1.2 g (7.12 mmol) ruthenium(IV)oxide hydrate in a mixture of 50 ml carbon tetrachloride and 50 ml water were added 9.0 g (42 mmol) sodium periodate. After stirring for 30 min the organic layer was separated and the aqueous layer was extracted twice with 10 ml portions of carbon tetrachloride. The combined organic layers were filtered over celite, cooled to 0°C and were added slowly to an ice-cooled solution of 2.0 g (3.54 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide in 20 ml carbon tetrachloride. The mixture was stirred for additional 15 min at 0°C, was filtered over celite and was evaporated. The residue was purified by flash-chromatography and gave 704 mg (34%) of the title compound as colourless foam.

MS m/e (%): 580 ($M+H^+$, 100).

Example 11

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(3-oxo-morpholin-4-yl)-pyridin-3-yl]-N-methyl-isobutyramide

The title compound was obtained as light brown oil in comparable yields according to the procedures described above for the preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide.

MS m/e (%): 600 ($M+H^+$, 100).

Example 12

Acetic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester

a) N2-Benzyl-N5-methyl-4-o-tolyl-pyridine-2,5-diamine

The title compound was prepared following the procedures described above for the synthesis of methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine.

MS m/e (%): 304 ($M+H^+$, 100).

b) Benzyl-(5-methylamino-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester

To a solution of 2.03 g (6.7 mmol) N^2-benzyl-N^5-methyl-4-o-tolyl-pyridine-2,5-diamine in 100 ml dichloromethane and 40 ml N-ethyldiisopropylamine was added dropwise at 0°C a solution of 2.1 ml (14.09 mmol) benzyl chloroformate in 50 ml dichloromethane. After stirring for 2 h at room temperature the reaction mixture was washed with water (2 x 50 ml), brine (50 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 2.36 g (80%) of the title compound as light brown crystals. M.p. 110-112°C.

MS m/e (%): 438 ($M+H^+$, 100).

c) Benzyl-(5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester

To a solution of 1.075 g (2.5 mmol) benzyl-(5-methylamino-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester in 10 ml dichloromethane and 1 ml N-ethyldiisopropylamine was added dropwise at 0°C a solution of 1.15 g (3.5 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid chloride in 2 ml dichloromethane and the mixture was stirred for 3 h at room temperature. The solution was washed with water (20 ml), saturated aqueous sodium hydrogencarbonate solution (20 ml) and brine (20 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 1.15 g (62%) of the title compound as a yellow oil.

MS m/e (%): 720 ($M+H^+$, 100).

d) N-(6-Benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

To a solution of 973 mg (1.35 mmol) benzyl-(5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester in

13 ml methanol and 1 ml N,N-dimethylformamide was added 40 mg 10% palladium on activated charcoal and the mixture was hydrogenated (room temperature, 1 bar) for 1 h. Filtration of the catalyst and evaporation of the filtrate afforded 795 mg (quantitative) of the title compound as a yellow oil.

MS m/e (%): 586 ($M+H^+$, 100).

e) N-(6-Amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

A solution of 750 mg (1.28 mmol) N-(6-benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 25 ml of a 5 N solution of hydrochloric acid in ethanol was evaporated to dryness and the residue was dissolved in 30 ml methanol and hydrogenated in the presence of 60 mg 10% palladium on activated charcoal (room temperature, 10 bar) for 20 h. After filtration of the catalyst and evaporation of the solvent the residue was dissolved in 30 ml ethyl acetate, washed twice with saturated aqueous sodium hydrogencarbonate solution and dried (magnesium sulfate). Evaporation of the solution afforded 514 mg (81%) of the title compound as light brown crystals.

MS m/e (%): 496 ($M+H^+$, 100).

f) Acetic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester

To a solution of 100 mg (0.20 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 3 ml dichloromethane were added 27 mg (0.21 mmol) N-ethyldiisopropylamine and 30 mg (0.21 mmol) acetoxy acetyl chloride. After stirring overnight, the solvent was evaporated and the residue was purified by flash-chromatography to give 62 mg (52%) of the title compound as white solid.

MS m/e (%): 618 ($M+Na^+$, 19), 596 ($M+H^+$, 100).

Example 13

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-acetylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

To a solution of 30 mg (0.05 mmol) acetic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester in 2 ml tetrahydrofuran were added 2 ml 1 N sodium hydroxide solution at room temperature. After stirring for 15 min, ethyl acetate was added, the aqueous phase was separated and the

organic layer was dried (sodium sulfate). After evaporation the residue was purified by flash-chromatography to give 15 mg (54%) of the title compound as white solid.
MS m/e (%): 576 ($M+Na^+$, 19), 554 ($M+H^+$, 100).

Example 14

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(hydroxyacetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

To a solution of 70 mg (0.12 mmol) acetic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester in 4 ml tetrahydrofuran at room temperature under argon were added dropwise 0.13 ml (0.12 mmol) of a 1 M solution of potassium hexamethyldisilazide in tetrahydrofuran. Stirring was continued for 1 h at room temperature and 17 mg (0.12 mmol) methyl iodide were added. After stirring overnight, saturated ammonium chloride solution was added and the aqueous layer was extracted with diethyl ether. The diethyl ether layer was dried with sodium sulfate, evaporated, and the residue was purified by flash-chromatography to give 12 mg (18%) of the title compound as a white solid.

MS m/e (%): 590 ($M+Na^+$, 31), 568 ($M+H^+$, 100).

Example 15

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2,5-dioxo-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

To a solution of 100 mg (0.20 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 3 ml pyridine were added 54 mg (0.50 mmol) trimethylchlorosilane at room temperature. After stirring for 15 min, this mixture was added slowly under stirring to 155 mg (1.0 mmol) succinyl chloride and stirring was continued overnight. The solvent was removed *in vacuo* and the residue was purified by flash-chromatography to give 29 mg (25%) of the title compound as white solid.

MS m/e (%): 600 ($M+Na^+$, 16), 578 ($M+H^+$, 100).

Example 16

Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-cyclopropanecarbonyl-amide

To a solution of 100 mg (0.20 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 3 ml dichloromethane were added 29 mg (0.21 mmol) N-ethyldiisopropylamine and 46 mg (0.44 mmol) cyclopropanecarboxylic acid chloride at 0°C. After stirring overnight at room temperature, the solvent was removed *in vacuo* and the residue was purified by flash-chromatography to give 80 mg (63%) of the title compound as white solid.

MS m/e (%): 654 ($M+Na^+$, 30), 632 ($M+H^+$, 100).

Example 17

4-o-Tolyl-[2,3']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

The title compound was obtained as a white solid in comparable yield according to the procedure described above for the preparation of 4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide using 3-pyridylboronic acid instead of 4-pyridylboronic acid.

MS m/e (%): 530 ($M+H^+$, 100).

Example 18

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(2-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide

The title compound was obtained as a light brown solid in 99% yield according to the procedure described above for the preparation of 4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide using 2-methoxyphenylboronic acid instead of 4-pyridylboronic acid.

MS m/e (%): 559 ($M+H^+$, 100).

Example 19

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(3-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide

The title compound was obtained as a light yellow viscous oil in 81% yield according to the procedure described above for the preparation of 4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide using 3-methoxyphenylboronic acid instead of 4-pyridylboronic acid.

MS m/e (%): 559 ($M+H^+$, 100).

Example 20

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide

The title compound was obtained as a light yellow solid in 90% yield according to the procedure described above for the preparation of 4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide using 4-methoxyphenylboronic acid instead of 4-pyridylboronic acid.

MS m/e (%): 559 ($M+H^+$, 100).

Example 21

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(2-hydroxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide

To a solution of 80 mg (0.14 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-(2-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide in 1.5 ml dichloromethane 0.17 ml of a 1M solution of boron tribromide in dichloromethane (0.17 mmol) were added dropwise at 0°C. The temperature was allowed to warm to room temperature over night. Water and a 1M aqueous solution of hydrochloric acid were added. After 5 min the mixture was neutralized by addition of 1M aqueous sodium hydroxide solution and extracted with dichloromethane. The organic layer was dried with sodium sulfate and concentrated. Column chromatography afforded 67 mg (86%) of the title compound as a white solid.

MS m/e (%):545 ($M+H^+$, 100).

Example 22

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(3-hydroxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide

The title compound was obtained as a white solid in comparable yield according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-6-

(2-hydroxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide using N-(3,5-bis-trifluoromethyl-benzyl)-6-(3-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide instead of N-(3,5-bis-trifluoromethyl-benzyl)-6-(2-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide.

MS m/e (%):545 ($M+H^+$, 100).

Example 23

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(4-hydroxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide

To a solution of 80 mg (0.14 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-(2-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide in 1.5 ml dichloromethane 0.43 ml of a 1M solution of boron tribromide in dichloromethane (0.43 mmol) were added dropwise at 0°C. The cooling bath was removed and the mixture was stirred at 35°C over night. Water and a 1M aqueous solution of hydrochloric acid were added. After 5 min the mixture was neutralized by addition of 1M aqueous sodium hydroxide solution and extracted with dichloromethane. The organic layer was dried with sodium sulfate and concentrated. Column chromatography afforded 63 mg (81%) of the title compound as a white solid.

MS m/e (%):545 ($M+H^+$, 100).

Example A

Tablets of the following composition are manufactured in the usual manner:

	mg/tablet
Active substance	5
Lactose	45
Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

Example B

Capsules of the following composition are manufactured:

	mg/capsule
Active substance	10
Lactose	155
Corn starch	30
Talc	5
Capsule fill weight	200

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example C

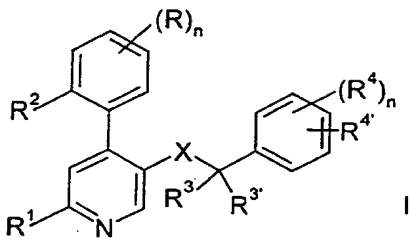
Suppositories of the following composition are manufactured:

		mg/supp.
Active substance		15
Suppository mass		1285
	Total	1300

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Claims

1. Compounds of the general formula

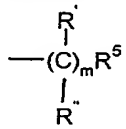


I

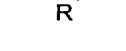
wherein

R is hydrogen or halogen;

R^1 is $-(C\equiv C)_mR^{1'}$ or $-(CR'=CR'')_mR^{1'}$
wherein $R^{1'}$ is
a) halogen,
b) cyano, or the following groups:

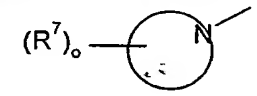


c)



,
d) $-C(O)NR'R''$,
e) $-C(O)O(CH_2)_mR^5$,
f) $-C(O)R^5$,
g) $-N(OH)-(CH_2)_mR^5$,
h) $-NR'C(O)-(CH_2)_mR^5$,
i) $-N[C(O)-R']_2$,
j) $-OR^6$,
k) $-SR^6$, $-S(O)R^6$, or $-S(O)_2R^6$,
l) aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R'', nitro, $-(CH_2)_nOR'$, -C(O)NR'R'', -C(O)OR' or -C(O)R',
m) is a five or six membered heteroaryl group, containing one to four heteroatoms, selected from N, O or S and may be optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy,

cyano, hydroxy, -NR'R'', nitro, -$(CH_2)_n$OR', -C(O)OR', -C(O)NR'R'' or –C(O)R', n) is a five or six membered saturated cyclic tertiary amine of the group



which may contain one additional heteroatom, selected from N, O or S,

R'/R'' are independently from each other hydrogen, lower alkyl, cycloalkyl or aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'''R'''', nitro, -$(CH_2)_n$OR''', -C(O)NR'''R'''', -C(O)OR''' or –C(O)R''',

R'''/R'''' are independently from each other hydrogen, lower alkyl, cycloalkyl or aryl,

R^5 is hydrogen, cyano, hydroxy, halogen, trifluoromethyl, -C(O)OR' or aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R'', nitro, -$(CH_2)_n$OR', -C(O)NR'R'', -C(O)OR' or –C(O)R', or is a five or six membered heteroaryl group, containing one to four heteroatoms, selected fron N, O or S and may be optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R'', nitro, -$(CH_2)_n$OR', -C(O)NR'R'', -C(O)OR' or –C(O)R',

R^6 is hydrogen, lower alkyl, trifluoromethyl, or aryl, optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R'', nitro, -C(O)NR'R'', -$(CH_2)_n$OR', -C(O)OR' or –C(O)R', or is a five or six membered heteroaryl group, containing one to four heteroatoms, selected fron N, O or S and may be optionally substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy, -NR'R'', nitro, -$(CH_2)_n$OR', -C(O)NR'R'', -C(O)OR' or –C(O)R',

R^7 is –C(O)-$(CH_2)_m$OH or an oxo group;

R^2 hydrogen, lower alkyl, lower alkoxy, halogen or CF_3;

$R^3/R^{3'}$ are independently from each other hydrogen, lower alkyl or form together with the carbon atom to which they are attached a cycloalkyl group;

$R^4/R^{4'}$ are independently from each other hydrogen, halogen, CF_3, lower alkyl or lower alkoxy;

R and R^2 or R^4 and $R^{4'}$ may be together –CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl, halogen or lower alkoxy;

X is $-C(O)N(R^8)-$, $(CH_2)_pO-$, $-(CH_2)_pN(R^8)-$, $-N(R^8)C(O)-$ or $-N(R^8)-(CH_2)_p-$; wherein R^8 is hydrogen or lower alkyl;

n is 1 or 2;

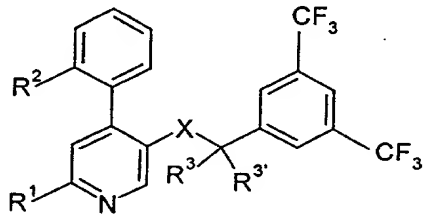
m is 0 to 4;

o is 1 or 2; and

p is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. A compound of formula IA according to claim 1,



IA

wherein

R^1 is halogen, $-(CH_2)_mCN$, -C(O)O-lower alkyl, $-(CH_2)_mOH$, $-N(OH)(CH_2)_mOH$, $-N(R)C(O)-(CH_2)_mOC(O)$-lower alkyl, $-N[C(O)\text{-cycloalkyl}]_2$, $-N(R)C(O)-(CH_2)_mOH$, pyridin-2,3,4-yl or phenyl, optionally substituted by lower alkyl, lower alkoxy or hydroxy or is morpholinyl or piperazinyl, substituted by $-C(O)-(CH_2)_mOH$ or oxy group(s),

R is hydrogen or lower alkyl;

R^2 is lower alkyl or halogen;

$R^3/R^{3'}$ are independently from each other hydrogen or lower alkyl;

X is $-C(O)N(R^8)-$ or $-N(R^8)C(O)-$;

R^8 is hydrogen or lower alkyl; and

m is 1 or 2;

3. A compound of formula I according to claim 1, wherein $-(R^4)_n$ is 3,5-di-trifluoromethyl.

4. A compound of formula I according to claim 3, wherein X is $-C(O)N(R)-$.

5. A compound of formula I according to claim 4, wherein $R^3/R^{3'}$ are both hydrogen and R^2 is methyl.

6. A compound of formula I according to claim 5, which is

N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-hydroxyacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-cyanomethyl-N-methyl-4-o-tolyl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-iodo-N-methyl-4-o-tolyl-nicotinamide,
4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
5-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-4-o-tolyl-pyridine-2-carboxylic acid methyl ester or
N-(3,5-bis-trifluoromethyl-benzyl)-6-hydroxymethyl-N-methyl-4-o-tolyl-nicotinamide.

7. A compound of formula I according to claim 3, wherein X is –N(R)C(O)-.

8. A compound of formula I according to claim 7, wherein $R^3/R^{3'}$ and R^2 are methyl.

9. A compound of formula I according to claim 8, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-{6-[hydroxy-(2-hydroxy-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide,
acetic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-acetylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(hydroxyacetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2,5-dioxo-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide or
cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-cyclopropanecarbonyl-amide.

10. A compound of formula I according to claim 7, wherein $R^3/R^{3'}$ are both hydrogen and R^2 is chloro.

11. A compound of formula I according to claim 10, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-{4-(2-chloro-phenyl)-6-[hydroxy-(2-hydroxy-ethyl)-amino]-pyridin-3-yl}-N-methyl-isobutyramide or

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(3-oxo-morpholin-4-yl)-pyridin-3-yl]-N-methyl-isobutyramide.

12. A compound of formula I according to claim 3, wherein X is $-N(R)-(CH_2)_p-$.

13. A compound of formula I according to claim 3, wherein X is $-(CH_2)_pO-$.

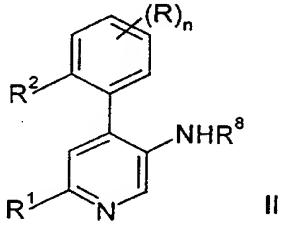
14. A compound of formula I according to claim 3, wherein X is $-(CH_2)_pN(R)-$.

15. A medicament containing one or more compounds as claimed in any one of claims 1-14 and pharmaceutically acceptable excipients.

16. A medicament according to claim 15 for the treatment of diseases related to NK-1 receptor antagonists.

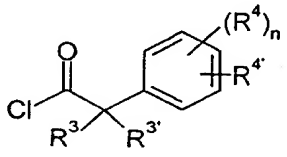
17. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



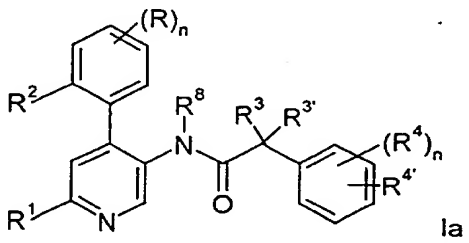
II

with a compound of formula



III

to a compound of formula

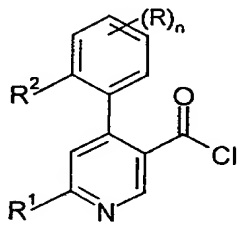


Ia

wherein R^1- R^4, R and n have the significances given above,

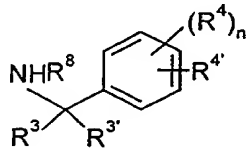
or

b) reacting a compound of formula



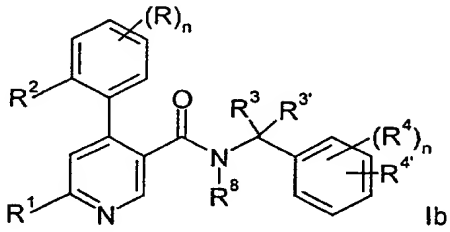
IV

with a compound of formula



V

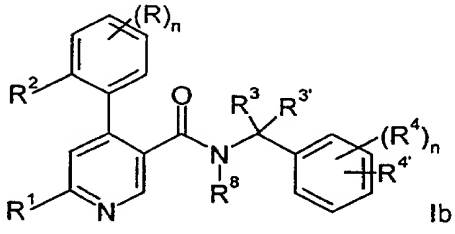
to give a compound of formula



Ib

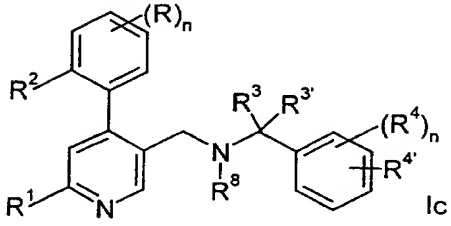
wherein R^1-R^4, R and n have the significances given above, or

c) reducing a compound of formula



Ib

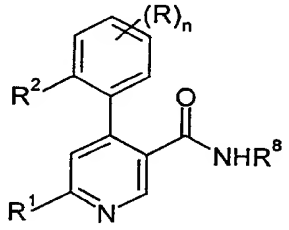
to a compound of formula



Ic

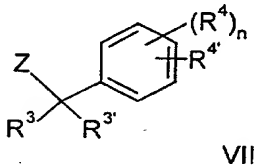
wherein the definition of substituents is given above, or

d) reacting a compound of formula



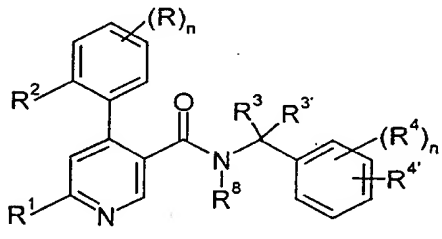
VI

with a compound of formula



VII

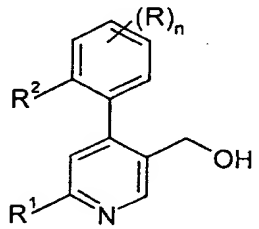
to a compound of formula



Ib

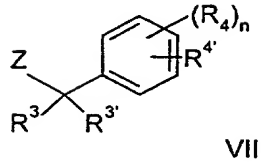
wherein Z is Cl, Br, I, $-OS(O)_2CH_3$ or $-OS(O)_2C_6H_4CH_3$ and the other definitions of substituents are given above, or

e) reacting a compound of formula



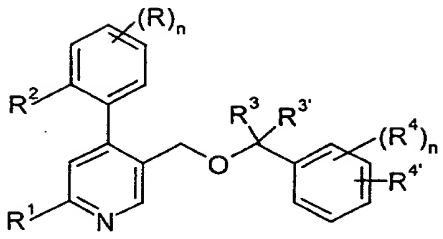
VIII

with a compound of formula



VII

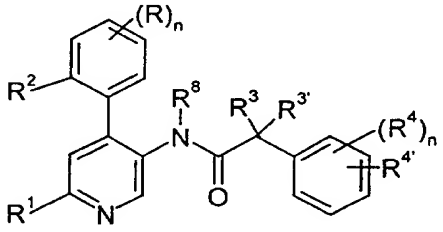
to a compound of formula



Id

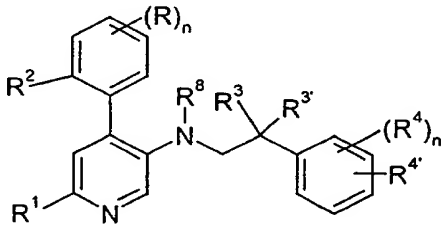
wherein Z is Cl, Br, I,- $OS(O)_2CH_3$ or $-OS(O)_2C_6H_4CH_3$ and the definition of the other substituents is given above, or

f) reducing a compound of formula



Ia

to a compound of formula



Ie

wherein the definition of substituents is given above,

or

h) modifying one or more substituents R^1-R^4, R^8 or R within the definitions given above, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

18. A compound according to any one of claims 1-14, whenever prepared by a process as claimed in claim 17 or by an equivalent method.

19. The use of a compound in any one of claims 1-14 for the treatment of diseases related to NK-1 receptor antagonists.

20. The use of a compound in any one of claims 1-14 for the manufacture of medicaments containing one or more compounds of formula I for the treatment of diseases related to NK-1 receptor antagonists.

21. The invention as hereinbefore described.

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